0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 1
Printed in U.S.A.

Editorial: Depot Somatostatin Analogs—A New First Line Therapy for Acromegaly

RICHARD J. ROBBINS

Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, New York 10021

In this issue of *JCEM*, two reports describe the first long-term follow-up studies of slow-release somatostatin analogs for the treatment of acromegaly. To appreciate the impact of these agents, it is helpful to look back at the evolution of somatostatin's role in acromegaly. Soon after the isolation of somatostatin by Vale and colleagues (1, 2), its ability to suppress GH levels in normal human volunteers was demonstrated. Hall *et al.* (3) showed that GH levels in acromegalics were clearly suppressed during somatostatin infusions. Within the next ten yr, additional studies demonstrated that somatostatin could also reduce serum levels of insulin-like growth factor I (IGF-I), insulin, glucagon, thyrotropin (TSH), prolactin, and many other neuroendocrine peptides. An interesting report by Pieters *et al.* (4) found that GH levels in some acromegalics were easily suppressed by somatostatin infusions, while in others only a minimal decline in GH ensued. The apparent diversity in response to somatostatin was initially ascribed to the wide variation in the number of somatostatin receptors on human somatotrophic adenoma membranes (5, 6).

This favorable GH response to somatostatin in acromegaly quickly created a new problem. The rapid degradation of the native tetradecapeptide by peptidases reduced its effective half-life to several minutes. With such clinically relevant activity, biochemists quickly took up the task of creating a less labile version of somatostatin (7). In 1984, Plewe and colleagues (8) reported on the ability of a Sandoz compound, SMS 201-995 (now known as octreotide), to induce a prolonged GH suppression in acromegalic subjects. These observations were quickly confirmed, and a new clinically useful medical therapy for acromegaly was born. The GH lowering ability of a single injection of octreotide could last as long as ten h. When treated with two or three injections daily, the first group of acromegalics noted resolution of headache, soft tissue swelling, nerve entrapment symptoms, and sweating. An unexpected bonus was the observation that shrinkage of the pituitary adenomas occurred in many of the patients. When compared with the only other medical therapy for acromegaly at that time, bromocriptine, octreotide was much more effective. In addition, some individuals who responded poorly to either agent had a clear response to the combination of bromocriptine and octreotide (9).

By the late 1980s, a new standard in the therapeutic approach to acromegaly had been established (10). The primary approach to the vast majority of the patients would be surgical removal of the pituitary tumor, with radiation therapy of any residual tumor that could not be resected. Octreotide and/or bromocriptine were reserved for surgical failures or to control symptoms while the radiation therapy slowly lowered GH production. This subordinate role for octreotide was due in part to the necessity for multiple daily injections and because of the occurrence of side effects including injection site pain, an increased incidence of gallstones, and diarrhea. More importantly, octreotide was not a cure, but merely a temporizing mechanism, while other more "definitive" treatments were being planned or were slowly working. On the positive side, it appeared that, once controlled, somatotropic tumors did not escape the inhibitory effects of octreotide, even after ten yr of continuous treatment (9).

As reported in this issue of *JCEM*, two research teams explored the potential usefulness of newer depot preparations of long-acting somatostatin analogs. Caron and colleagues (see page 18) (11) employed a slow release form of the cyclic octapeptide, BIM 23014 (somatuline; Ipsen Biotech), which has been named SR Lanreotide (SRL). In a group of 22 acromegalics (7 of whom had failed transsphenoidal surgery) who had been responding to treatment with octreotide, they found that 3 yr of SRL (30 mg im every 2 weeks) was able to lower GH and IGF-I levels to the normal or near normal range without escape. Approximately one third of the group, however, was unable to achieve normal GH or IGF-I levels. A number of individuals had to increase the injection frequency to every 10 days for optimal control. About half of the group had loose stools, nausea, and/or abdominal pain for the first 2 days after the injection. In this study, 18% of the subjects developed new gallstones while on SRL. In a separate report, Flogstad and collaborators (see page 23) examined the effects of a slow release form of octreotide (Sandostatin LAR; Sandoz Pharmaceuticals) given monthly to a group of 14 acromegalics who had previously demonstrated responsiveness to sc injections of octreotide. Many in this group had been previously treated with radiation, dopamine agonists, and/or octreotide. Only subjects who showed a clear suppression of GH following a prescreening challenge with octreotide were included in this study. Intramuscular doses of 20–40 mg were able to reduce GH and IGF-I to normal or near normal levels for 18 months,

Received September 30, 1996. Accepted October 6, 1996.
Address correspondence to: Richard Robbins, MD, Endocrinology Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021.

without escape. The maximum effect was achieved with a 30 mg dose of Sandostatin LAR. Side effects were similar to those reported by Caron *et al.* (11) with 1 of the 14 patients developing a gallstone during the treatment period. Importantly, in each of the 4 subjects who had never received octreotide, tumor shrinkage was documented. As in the study of Caron, signs and symptoms of acromegaly improved with treatment.

These two studies describe a significant advance in the therapy of acromegaly. First, the depot preparations seem to be as safe and efficacious as multiple sc octreotide injections. However, until daily multiple Sandostatin injections can be compared with the depot preparations in a clinical trial, the frequency of side effects and the ability to normalize GH and IGF-I will remain as qualitative impressions. Second, fewer injections will make patient acceptance more likely. Third, if efficacy of once-a-month injections can be confirmed, and if these agents are able to shrink adenomas, they should ultimately be compared to transsphenoidal surgery as possible first-line therapy. The previous experience with dopamine agonists in prolactinomas has shown that tumors that are reduced in size may have higher rates of spontaneous resolution. Of course, this effect may be uniquely related to bromocriptine. However, if shrinkage of a somatotrophic tumor is achieved, it seems reasonable to monitor such a group of acromegalics for several years to see if the rate of spontaneous resolution is higher than previously reported (13). Interestingly, shrinkage of somatotrophic adenomas does not seem to correlate with GH suppression (14), but may be related to somatostatin receptors on tumoral blood vessels (15).

Although the results of these studies are promising, neither compound is widely available. SR Lanreotide is currently available in France and will soon be available in other Western European countries. Neither compound is currently available in the USA. Each pharmaceutical company is highly committed to the process of approval through appropriate government agencies. Manufacturing problems may delay the availability of Sandostatin LAR in the USA for two years. Nevertheless, endocrinologists will soon have additional options for dealing with a newly diagnosed acromegalic.

Selective transphenoidal adenomectomy still seems the best option for a young patient with a microadenoma. For small tumors, cure rates as high as 80% exist in the hands of experienced surgeons (16). All newly diagnosed acromegalics should have a standard challenge of octreotide to identify nonresponders. Depot preparations of somatostatin analogs should be considered first line therapy for responders who are older, who have invasive adenomas, who do not want to risk central hypogonadism, and who refuse a surgical approach. For these groups, the option of a depot somatostatin analog may be safer than radiation therapy. The prolonged time to cure, the high incidence of hypopituitarism (17), and the possibility of optic nerve damage or subsequent brain tumors (18) makes conventional linear accelerator radiation much less attractive. Newer, more highly concentrated irradiation techniques are currently being tested; however, their safety and efficacy remain to be defined in acromegaly.

Is the GH lowering reported in these trials sufficient? Newer GH assays have now demonstrated that "normal" levels of human GH are much lower than previously recognized. Do GH levels have to be normal for the complications of acromegaly and the reduced life span to be eliminated? One preliminary study has suggested that normal survival occurs in acromegalics with post-treatment GH levels below 2.5 ng/mL, but not in those with higher GH levels (19). Until further studies are conducted, it seems that additional therapy should be considered in those whose GH levels are above 5 ng/mL or whose IGF-I levels are above normal while on somatostatin analogs.

Are these the best analogs? At least five different types of somatostatin receptors exist. All five are expressed in normal somatotrophs (20), and all five have been found in somatotropic tumors (21). Octreotide and lanreotide act predominantly at the type 2 and 5 receptors, which are the subtypes with the highest expression in somatotropic tumors. The lack of escape from these analogs may be due to the fact that these receptors do not downregulate on chronic exposure to somatostatin (22). However, 15–20% of acromegalics do not respond well to octreotide, raising the possibility that altered expression or regulation of the receptor subtypes is present. Because acromegaly is uncommon, our patients would be well served if the pituitary community designed a multicenter controlled trial of depot somatostatin preparations against transphenoidal surgery for primary therapy of acromegaly. It may be difficult for this trial to be blinded or randomized, but rigorous pre-operative and post-operative clinical, radiological, and biochemical evaluations will be essential. These new therapeutic tools are on the horizon, and research with them will hopefully open up new perspectives into the biology of somatotropic adenomas and the clinical management of acromegaly.

Acknowledgments

I would like to thank my colleagues at Memorial Hospital, Yale University, and members of the Pituitary Society for continued support. The editorial comments of Seymour Reichlin, Anne Robbins, and Cherryl Murray-Marone were very helpful.

References

1. **Vale W, Brazeau P, Grant G, et al.** 1972 Premieres observations sur le mode d'action de la somatostatine, un facteur hypothalamique qui inhibe la secretion de l'hormone de croissance. C R Acad Sci (Paris). 275:2913–2915.
2. **Brazeau P, Vale W, Burgus R, Ling M, Rivier Y, Guillemin R.** 1973 Hypothalamic peptide that inhibits the secretion of immunoreactive growth hormone. Science. 179:77–79.
3. **Hall R, Besser GM, Schally A, et al.** 1973 Actions of growth hormone release inhibitory hormone in healthy men and in acromegaly. Lancet. 2:581–584.
4. **Pieters G, Romeijn J, Smals A, Kloppenborg P.** 1982 Somatostatin sensitivity and growth hormone responses to releasing hormones and bromocriptine in acromegaly. J Clin Endocrinol Metab. 54:942–949.
5. **Ikuyama S, Nawata H, Kato K, Karashima T, Ibayashi H, Nakagaki J.** 1985 Specific somatostatin receptors on human pituitary adenoma cell membranes. J Clin Endocrinol Metab. 61:666–671.
6. **Moyse E, Le Dafniet M, Epelbaum J, et al.** 1985 Somatostatin receptors in human growth hormone and prolactin secreting pituitary adenomas. J Clin Endocrinol Metab. 61:98–103.
7. **Bauer W, Briner U, Doepfner W, et al.** 1982 SMS 201-995: a very potent and selective analog of somatostatin with prolonged action. Life Sci. 31:1133–1136.
8. **Plewe G, Beyer J, Krause U, Neufield M, del Pozo E.** 1984 Long-acting and selective suppression of GH secretion by somatostatin analog SMS 201–995 in acromegaly. Lancet. 2:782–787.
9. **Lamberts S, van der Lely A, de Herder W, Hofland L.** 1996 Octreotide. N Engl J Med. 334:246–254.
10. **Melmed S.** 1990 Acromegaly. N Engl J Med. 322:966–977.
11. **Caron P, Morange-Ramos I, Cogne M, Jaquet P.** 1997 Three year follow-up

of acromegalic patients treated with intramuscular slow-release lanreotide. J Clin Endocrinol Metab. 82:18–22.
12. **Fløgstad AK, Halse J, Bakke S,** *et al.* Sandostatin LAR in acromegalic patients: long term treatment. J Clin Endocrinol Metab. 82:23–28.
13. **Login I, Santen R.** 1975 Empty sella syndrome: Sequela of the spontaneous remission of acromegaly. Arch Int Med. 135:1519–1522.
14. **Plockinger U, Reichel M, Fett U, Saeger W, Quabbe H.** 1994 Preoperative octreotide treatment of growth hormone-secreting and clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab. 79:1416–1423.
15. **Reubi J, Schaer J, Laissue J, Waser B.** 1996 Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels. Metabolism. 45 [Suppl. 1]:39–41.
16. **Tindall G, Oyesiku N, Watts N, Clark R, Christy J, Adams P.** 1993 Transphenoidal adenomectomy for growth hormone-secreting pituitary adenomas in acromegaly: outcome analysis and determinants of failure. J Neurosurg. 78:205–215.
17. **Gordon P, Glatstein E, Oldfield E, Roth J.** 1987 Conventional supervoltage radiation in the treatment of acromegaly. In: Robbins RJ, Melmed S, eds. Acromegaly: A century of scientific and clinical progress. New York and London: Plenum Press; 211–220.
18. **Brada M, Ford D, Ashley S, et al.** 1992 Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma. British Medical Journal. 304:1343–1346.
19. **Bates A, Van't Hoff W, Jones J, Clayton R.** 1995 Does treatment of acromegaly affect life expectancy? Metabolism. 44 [Suppl 1]:1–5.
20. **Day R, Dong W, Panetta R, Kracier J, Greenwood M, Patel Y.** 1995 Expression of mRNA for somatostatin receptors subtypes 2 and 5 in individual rat pituitary cells. Endocrinology. 136:5232–5235.
21. **Patel Y, Greenwood M, Panetta R, et al.** 1996 Molecular biology of somatostatin receptor subtypes. Metabolism. 45 [Suppl. 1]:31–38.
22. **Hukovic N, Panetta R, Kumar U, Patel Y.** 1996 Agonist-dependent regulation of cloned human somatostatin receptor types 1–5: subtype selective internalization or up-regulation. Endocrinology. 137:4046–4049.